36 An Integrated Clinicopathologic Approach to Ever-Confusing Thyroid Pathology

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2011 Annual Meeting – Las Vegas, NV

AMERICAN SOCIETY FOR CLINICAL PATHOLOGY
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This session will cover several aspects of thyroid cytology and histology of follicular derived lesions. Practical hints will be offered, based on the presenter's experience and literature that can aid in the diagnosis of fine-needle aspiration specimens, intraoperative consultations, as well as histology. Discussions will include conventional histopathology and immunohistochemical and molecular diagnostic tools as well as the therapeutic and prognostic implications of various diagnoses. A practical and reproducible approach to the proposed Bethesda diagnostic terminology for thyroid cytology will be presented with follow-up data and statistics as well as the role of molecular reflex testing on thyroid FNA specimens.

- Apply current diagnostic categories in thyroid cytology and histology.
- Identify the role of special studies (Immunohistochemistry and molecular markers) in the diagnosis of thyroid lesions.
- Discuss the clinical implications of pathologic diagnosis of follicular derived thyroid lesions.

FACULTY:

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Practicing Pathologists
Surgical Pathology
Surgical Pathology (Derm, Gyn, Etc.)

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Update on the Pathology of the Thyroid Tumors

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Prevalence of Thyroid Nodules
Thyroid Lesions
Controversial?

_Follicular patterned lesions_

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The term “Follicular”

- Cell of origin
  - Capable of producing thyroid hormone and thyroglobulin
- Architecture / growth pattern
  - Follicular – totally or >95% of the lesion displays a follicular growth pattern.
  - Microfollicular
  - Macrofollicular

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Follicular Patterned Lesions

- Diagnosis and Classification
  - Cytology
  - Surgical Pathology
    - Histologic Diagnosis
    - Ancillary techniques
Follicular Patterned Lesions

Cytologic Diagnosis & Classification

Follicular Patterned Lesions of Thyroid

- Cytology – Reality Check
  - Cannot differentiate between follicular adenoma and carcinoma
  - Most are diagnosed as “Follicular Lesion / Neoplasm”
  - Up to 80% of cases diagnosed as such are benign on histologic examination (hyperplastic nodule or adenoma)
  - Approximately half of malignant cases are follicular variant of papillary carcinoma

Diagnosing Follicular Lesion/Neoplasm

Morphologic Criteria
The Usual Teaching

- Monolayer sheets of follicular cells
  - Benign

- Microfollicles
  - Neoplasm / Lesion
  - Micro-follicular lesion

- Atypical Follicular cells
  - Neoplasm / Lesion

Is It That Easy

Don’t Think So

Monolayer Sheet

- Sheet of cells arranged in a layer or loosely cohesive group
- Due to presence of large follicles
  - Goiter
  - Papillary carcinoma
    - Follicular variant
    - Follicular carcinoma
Microfollicles

• Define and measure the size of follicle

Microfollicles

I Don't Think So

Microfollicles

• Inter-observer Agreement on Microfollicles
  – Renshaw AA et al. (Arch Pathol Lab Med 2006)
  – 12 cytopathologists were shown 45 small groups of follicular cells
    • 20 Microfollicles
    • 7 Macrofollicles
    • 18 Indeterminate
  – <15 cells arranged in circle that is at least two-thirds complete, should be classified as microfollicles.

Microfollicles

• Mowschenson PM et al (Surgery 1994)
• FNA of normal thyroid tissue may result in the misdiagnosis of micro-follicular lesions
  – 42 cases
    • 9 unremarkable
    • 18 microfollicular
    • 3 mixed macromicrofollicular
    • 1 Hurthle cell
    • 1 Papillary carcinoma
Cytomorphology: Follicular Neoplasm

Diagnosis
Follicular Lesion / Neoplasm

Diagnosis
Follicular Lesion / Neoplasm
The Bethesda System for Reporting Thyroid Cytopathology: Implied Risk of Malignancy and Recommended Clinical Management

<table>
<thead>
<tr>
<th>Diagnostic Category</th>
<th>Risk of Malignancy (%)</th>
<th>Usual Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nondiagnostic or Unsatisfactory</td>
<td></td>
<td>Repeat FNA with ultrasound guidance</td>
</tr>
<tr>
<td>Benign</td>
<td>0-3%</td>
<td>Clinical follow-up</td>
</tr>
<tr>
<td>AUS (Atypia of Undetermined Significance) or FLUS (Follicular Lesion of Undetermined Significance)</td>
<td>~5-15%</td>
<td>Repeat FNA</td>
</tr>
<tr>
<td>Follicular Neoplasm or Suspicious for a Follicular Neoplasm (Specify if Hurthle type or Oncocytic)</td>
<td>15-30%</td>
<td>Surgical lobectomy</td>
</tr>
<tr>
<td>Suspicious for Malignancy</td>
<td>60-75%</td>
<td>Near-total thyroidectomy or surgical lobectomy</td>
</tr>
<tr>
<td>Malignant</td>
<td>97-99%</td>
<td>Near-total thyroidectomy</td>
</tr>
</tbody>
</table>

Follicular Lesion Histology

- Controversial Diagnosis
  - Adenoma vs. Follicular carcinoma vs. Follicular variant of papillary carcinoma
  - Lloyd RV et al. AJSP 2004 (28)
    - A concordant diagnosis of FVPCA was made by all 10 reviewers with a cumulative frequency of 39%.
    - In this series, 24.1% of the patients had metastatic disease (n = 21). In the cases with metastatic disease, a diagnosis of FVPCA was made by all 10 reviewers with a cumulative frequency of 66.7%.
  - Elshiekh TM et al. AJCP 2008
    - 15 cases of FVPCA – unanimous agreement in 2 (13%)
Follicular Carcinoma Diagnosis

Capsular invasion only
- Associated with metastatic disease
  - Khan & Perzin; Evans et al
- Tumors with capsular invasion also demonstrate foci of vascular invasion on extensive sectioning of the tumor capsule
  - Yamashina et al

Follicular carcinoma

- Diagnosis based on invasive characteristics
  - Capsular invasion
  - Vascular invasion

Follicular Carcinoma Diagnosis

Capsular Invasion – Diagnosis

- Tumor cells invading into and through the capsule into the surrounding thyroid parenchyma.
Oncocytic (AKA Hurthle cell) & Follicular Carcinoma Diagnosis

Capsular Invasion – Diagnosis
• Tumor cells invade into the tumor capsule only without invasion into surrounding thyroid.
  – Tumor cells mushroom out into the capsule
  – Tumor cell invade into a hook-like pattern, usually horizontally into the capsule.

Oncocytic (AKA Hurthle cell) & Follicular Carcinoma Diagnosis

• Vascular invasion with or without capsular invasion
  – Angio-invasive Hürthle cell / Follicular carcinoma
Follicular Variant of Papillary Carcinoma (FVPTC)

First described by Lindsay in 1960
Chen and Rosai in 1977
- Proposed the term FVPTC
- Biologic similarities to conventional Pap Ca
- Follicle formation with nuclear features of Pap Ca
- Capsular and/or vascular invasion (20%)
**FVPTC**

*Diagnostically challenging cases*

- Encapsulated, no invasive features
- Seen in a background of nodular goiter
- Show admixture of micro and macro follicles
- Consists of areas diagnostic of papillary carcinoma and areas that appear benign
Well-differentiated Tumor of Uncertain Malignant Potential (WTUMP)
Williams et al

Encapsulated follicular patterned lesions
• Minor nuclear changes of PTC
• Minor capsular penetration without nuclear changes of PTC
• Borderline diagnosis
• Extremely good prognosis

• Advantages
  – Conservative treatment
    • Adequate resection should be enough
    • Avoidance of radioactive iodine treatment
Well-differentiated Tumor of Uncertain Malignant Potential
Williams et al

Disadvantages
• Lack of commitment on the part of pathologist
• Treatment ???
  — Lack of data (long term follow-up)
  — Published cases which have shown distant metastasis
  • Khan and Perzin, Evans, Baloch & LIVolsi

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Follicular Variant
of Papillary Thyroid Carcinoma
(FVPTC)

Histologic Scenarios

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FVPTC Histologic Scenarios

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FVPTC Histologic Scenarios

FVPTC Histologic Scenarios

FVPTC Histologic Scenarios
Important Questions/Issues?

- Is the current management of encapsulated FVPTC too aggressive?
  - Yes
- Is the diagnosis “WDTUMP” justifiable?
  - ?
- Role of immunohistochemical and molecular markers in the diagnosis of PTC

Clinicopathologic Data

Modify the current management of Encapsulated FVPTC

FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- Two Types:
  - Infiltrative
  - Encapsulated
FOLLICULAR VARIANT OF PAPILLARY CARCINOMA

- Statistically significant differences between two types:
  - Lymph node mets 65% vs 5%
  - ETE 65% vs 5%
  - Positive margins 50% vs 2%

- NO NONINVASIVE ENCAPSULATED TUMORS WERE AGGRESSIVE EVEN WITH JUST LOBECTOMY (11 years f/u)!!

Encapsulated FVPTC

- Memorial study (Thyroid 2009)
  - 43 Encapsulated classical PTC
  - 63 Encapsulated FVPTC
  - Median F/U 8.3 yrs

- Distant metastasis in 4 FVPTC with extensive capsular and vascular invasion.
- No recurrence in non-invasive FVPTC
  - 30 patients treated by lobectomy and no RAI

FVPTC F/U HUP Study

(Baloch et al. Endo Practice 2010)

- 42 cases of FVPTC 1997-1978
- 25 cases with mean F/U 7.7 yrs
- 1 recurrence (4%)
  - Rib metastasis after 7.3 yrs – encapsulated FVPTC no invasion.
The Quest for a Magic Marker?

*Immunohistochemistry*
**Thyroid Tumor Microarray Study**

Coexpression and concurrent absence of expression of immunohistochemical stain panels

<table>
<thead>
<tr>
<th>Stain Panel</th>
<th>Malignant (n=37)</th>
<th>Benign (n=53)</th>
<th>Sensitivity for Carcinoma</th>
<th>Specificity for Carcinoma</th>
</tr>
</thead>
<tbody>
<tr>
<td>HBME+, CK19+, GAL+</td>
<td>20</td>
<td>0</td>
<td>50%</td>
<td>100%</td>
</tr>
<tr>
<td>P16+, ERK+, RET+</td>
<td>19</td>
<td>6</td>
<td>51%</td>
<td>99%</td>
</tr>
<tr>
<td>Concurrent Absence</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HBME-, CK19-, GAL-</td>
<td>0</td>
<td>20</td>
<td>38%</td>
<td>100%</td>
</tr>
<tr>
<td>P16-, ERK-, RET-</td>
<td>0</td>
<td>15</td>
<td>28%</td>
<td>100%</td>
</tr>
</tbody>
</table>

**Role of Molecular Markers in The Diagnosis of Thyroid Lesions**

**The Challenge for Diagnostic Pathologists**

*Practicing Morphology in the Molecular Age*
“Pathways” in the Development of Papillary Carcinoma
Tallini G. Endocrine Pathology 2002

Mutations in Papillary Carcinoma

- BRAF 45%
- RET/PTC 15%
- RAS 15%

~75% Papillary CA

- Tall cell and classical papillary CA
- Extra-thyroidal extension
- Higher stage at presentation
- Higher rate of tumor recurrence
- Propensity to de-differentiation

Mutations in Papillary Carcinoma

- Classic papillary CA
- Younger age at presentation
- Assoc. with radiation exposure
- Frequent lymph node metastasis
- Lower stage at presentation

- Follicular variant of PTC
- Frequent encapsulation
- Less frequent node metastasis
- More frequent distant metastases
BRAF & Papillary Carcinoma

- BRAF mutations can occur early in the development of PTC
  - Present in micro-PTC (Nikiforova et al)

- PTC with BRAF mutations have more aggressive properties – advanced clinical stage (tall cell variant)

- Anaplastic and Poorly differentiated carcinoma arising from PTC have a significant prevalence of BRAF mutations (Lupi et al. JCEM 2007)

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BRAF Mutations in Thyroid Nodules:
Prevalence and Specificity

<table>
<thead>
<tr>
<th></th>
<th>Benign Nodules</th>
<th>Follicular Carcinoma</th>
<th>Papillary Carcinoma</th>
<th>PDC and AC</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of cases reported</td>
<td>611</td>
<td>171</td>
<td>2140</td>
<td>125</td>
</tr>
<tr>
<td>BRAF V600E</td>
<td>1 (0.16%)</td>
<td>0</td>
<td>45% (30-83%)</td>
<td>21% (0-50%)</td>
</tr>
</tbody>
</table>

_meta-analysis of literature 2003-2007_

BRAF V600E Predicts Tumor Aggressiveness

- Multicenter study, 107 patients
- Single institution, 100 patients

Xing et al. JCEM (2005)  
Elisei R et al. JCEM (2008)
**Histotype** | **BRAF V600E-positive cases**
---|---
**Micro PTC** |  
Encapsulated | 11/57 (19.3%) |
Not encapsulated | 79/173 (45.7%) |
**FV PTC** |  
Encapsulated | 5/52 (9.6%) |
Not encapsulated | 13/21 (61.9%) |
**CV PTC** |  
Encapsulated | 16/62 (25.8%) |
Not encapsulated | 43/61 (70.5%) |
**TCV PTC** |  
Encapsulated | 32/40 (80.0%) |
Not encapsulated | 1/8 (12.5%) |
**Others** |  
Encapsulated | 14/26 (53.8%) |
Not encapsulated |  |  

**Unusual Exon 15 BRAF Mutations in Papillary Carcinoma**

<table>
<thead>
<tr>
<th>Protein change</th>
<th>Nucleotide change</th>
<th>Histologic Variant</th>
<th>Frequency</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>K601E</td>
<td>A1801G</td>
<td>Follicular variant of PTC, unspecified variant (1)</td>
<td>5/54 (7%)</td>
<td>Lim et al, 2004; Oehler et al, 2005; Trovicsco et al, 2005</td>
</tr>
<tr>
<td>V599Ins</td>
<td>GTT</td>
<td>Conventional variant</td>
<td>Single case</td>
<td>Monaster et al, 2006</td>
</tr>
<tr>
<td>V599del-</td>
<td>1799del</td>
<td>PTC, unspecified variant</td>
<td>Single case</td>
<td>Monaster et al, 2006</td>
</tr>
<tr>
<td>T599I-</td>
<td>VKSR600-</td>
<td>3del</td>
<td>Single case</td>
<td>Monaster et al, 2006</td>
</tr>
<tr>
<td>A598V</td>
<td>C1793T</td>
<td>Follicular variant of PTC</td>
<td>Single case</td>
<td>Santarpia et al, 2009</td>
</tr>
</tbody>
</table>

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**PTC**

**Follicular Adenoma**

**Follicular cell**

**PDCA**

**Anaplastic Ca**

**Follicular carcinoma**

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**BRAF, RET-PTC, RAS**
Mutations in Follicular Carcinoma

\[ \text{RAS} \rightarrow \text{FA} \rightarrow \text{PC} \rightarrow \text{~70% Follicular CA} \]

\[ \text{PAX8-PPAR}\gamma \rightarrow 40\% \text{ Follicular CA} \]

\[ \text{30\% Follicular CA} \]

Molecular Analysis of FVPTC

- Hybrid tumor which shares molecular properties of papillary and follicular carcinoma.
  - BRAF (V600E, K601E, A598V)
  - RAS mutations (43%)
  - PPAR-gamma

Molecular Testing of Thyroid FNA Specimens

1. Role of Reflex Molecular Testing of Thyroid FNA specimens
2. Home Brewed Tests vs. Commercially Available Tests
BRAF Mutations in Thyroid FNA Samples

<table>
<thead>
<tr>
<th>Samples (n)</th>
<th>BRAF Positive</th>
<th>Final Diagnosis in BRAF Positive Samples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid Nodule FNA 9 Prospective Studies</td>
<td>1,814</td>
<td>159</td>
</tr>
<tr>
<td>Thyroid Nodule FNA 7 Retrospective Studies</td>
<td>685</td>
<td>291</td>
</tr>
<tr>
<td>Research FNA of Surgically Removed Thyroid, 2 studies</td>
<td>267</td>
<td>131</td>
</tr>
<tr>
<td>Total, 18 studies</td>
<td>2,766</td>
<td>581</td>
</tr>
</tbody>
</table>

*Hyperplastic nodule reported as “atypical nodular hyperplasia”

PTC - Papillary Thyroid Carcinoma

Nikiforova MN & Nikiforov YE, Thyroid

Testing for Multiple Mutations in Thyroid FNA Samples

- Prospective study, 2003-2006, two centers (Univ. of Cincinnati, Univ. of Colorado)
- Thyroid nodule tested: 470
- Mutation detected: 32

<table>
<thead>
<tr>
<th>Mutation</th>
<th>Risk of Cancer</th>
</tr>
</thead>
<tbody>
<tr>
<td>BRAF (18)</td>
<td>100%</td>
</tr>
<tr>
<td>RAS (8)</td>
<td>87%</td>
</tr>
<tr>
<td>RET/PTC (5)</td>
<td>100%</td>
</tr>
<tr>
<td>PAX8/PPARγ (1)</td>
<td>100%</td>
</tr>
</tbody>
</table>

Nikiforov et al. JCEM (2009)

Performance of molecular testing in specific categories of indeterminate FNA cytology

Nikiforov, Y. E. et al. 2009:94:2092-2098. JCEM
<table>
<thead>
<tr>
<th>Results of Cytology and Molecular Analysis</th>
<th>Cancer Probability in Thyroid Nodules</th>
</tr>
</thead>
<tbody>
<tr>
<td>Positive Cytology and Positive for Mutation</td>
<td>100%</td>
</tr>
<tr>
<td>Indeterminate Cytology Alone</td>
<td>40.4%</td>
</tr>
<tr>
<td>Indeterminate Cytology and Positive for Mutation</td>
<td>100%</td>
</tr>
<tr>
<td>Indeterminate Cytology and Negative for Mutation</td>
<td>16.2%</td>
</tr>
<tr>
<td>Negative cytology Alone</td>
<td>2.1%</td>
</tr>
<tr>
<td>Negative cytology and Negative for Mutation</td>
<td>0.9%</td>
</tr>
</tbody>
</table>

Nikiforov et al. JCEM (2009)

The Business of Thyroid FNA Molecular Tests

*Already here and probably more on their way.*

Asuragen

- Austin, Texas – April 6, 2011. Asuragen, Inc. announced today the launch of Inform™ Thyroid, a panel of molecular markers used on Fine Needle Aspirates (FNA) of thyroid nodules to aid physicians in the management of thyroid cancer.
- The FNAs are analyzed in Asuragen’s CAP accredited CLIA Laboratory.
- The Revised American Thyroid Association Management Guidelines for Patients with Thyroid Nodules and Differentiated Thyroid Cancer has stated, “The use of molecular markers (e.g., BRAF, RAS, RET/PTC, Pax8-PPARγ) may be considered for patients with indeterminate cytology on FNA to help guide management.”
Indeterminate results on thyroid FNA samples are a common and significant problem for physicians and their patients. FNA samples can be challenging to interpret and produce inconclusive results in up to 30 percent of cases. Current guidelines recommend that most of these patients go to surgery. However, the majority of these cases end up being benign. Now, the Afirma Thyroid FNA Analysis delivers physicians an improved solution to better assess thyroid nodules. The Afirma Thyroid FNA Analysis combines expert cytopathology and the novel Afirma Gene Expression Classifier.

Veracyte - Test
Complex Biology of Thyroid Neoplasm Subtypes Requires High-dimensionality Genomic Data

Whole Transcriptome approach using microarray technology
Molecular Classifier trained and validated to distinguish Benign vs. Suspicious Nodules
A multidimensional algorithm required to separate complex data sets

Benign
Suspicious
One new test shows early promise, as unveiled recently in an online posting of a *Journal of Clinical Endocrinology & Metabolism* paper* and in a presentation at the 14th International Thyroid Congress meeting in Paris, France. Produced by researchers at the South San Francisco-based Veracyte, Inc., the test is undergoing clinical trial at nearly 50 medical sites throughout the United States.
Current Sites for Thyroid FNA Sample Triage for Veracyte, INC

Specialization and Experience Result in Better Patient Care

Thyroid Cytopathology Partners, the thyroid nodule experts, offer:
Analysis by academic-caliber, thyroid-only cytopathologists

Clear, consistent and actionable Patient Reports
Patient case review (upon request) The beneficiaries of our expertise are physicians and their patients

Thyroid Cytopathology Partners is partnered with Veracyte, the South San Francisco-based leader in molecular cytology, to provide cytopathology review for samples submitted for the Afirma® Thyroid FNA Analysis. We have assembled a highly-trained, expert group of cytopathologists who exclusively review thyroid nodule FNAs, ensuring exposure to both common and rare thyroid lesions.

Few Questions & More

• How good is your diagnosis
• Patient management
• Case selection
  — All or few
• Economic effects

Conclusions

Pathologist in the front seat

Diagnosis of Thyroid Tumors
Multi-modality Approach
Diagnosis of Thyroid Tumors

- Clinical presentation and radiologic findings
- Cytologic diagnosis
  - Molecular analysis of selected cases
- Type of Surgery
  - Lobectomy vs. Total thyroidectomy
  - Lymph node excision (sampling, dissection)
- Management + Molecular analysis
  - Radioactive iodine treatment Yes or no

PAPILLARY THYROID LESIONS

Virginia A. LiVolsi, MD
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Philadelphia, PA

- To be discussed
  - Papillary hyperplasia (Graves disease)
  - Papillary hyperplastic nodule
  - Papillary carcinoma and variants
GRAVES’ DISEASE

- **CLINICAL**
  - Female: male=10:1
  - Goiter
  - Toxicity
  - Autoimmune
  - Familial
GRAVES’ DISEASE

• GROSS
  – Diffuse enlargement
  – Vascularity
  – Smooth capsule
  – Reddish brown

GRAVES’ DISEASE

• MICROSCOPIC
  – Lobulation
  – Papillary hyperplasia
  – Cell hypertrophy
  – Decreased colloid
  – Scalloping
  – Stromal lymphocytes
  – Clear, enlarged nuclei -- ROUND
GRAVES' DISEASE

- MICROSCOPIC
  - LONGSTANDING
    - Fibrosis
    - Hurthle cell metaplasia
    - Random nuclear atypia (dark, enlarged, irregular)
GRAVES’ DISEASE

• IMMUNOPATHOLOGY
  — Gland B:T cell ratio 50:50
  — Peripheral blood B:T cell 20:80
  — TSH receptor antibodies

GRAVES’ DISEASE

• PATHOPHYSIOLOGY
  — Antibodies fool the TSH receptor on follicular cells
  — Follicular cells grow and divide
  — Hyperfunction, hyperplasia, hypertrophy
  — Increase thyroid hormone
  — Decrease storage
  — Suppress TSH
HYPERTHYROIDISM I

- CAUSES OTHER
  - Toxic nodular goiter
  - Chronic lymphocytic thyroiditis (some)
  - Functioning neoplasms (adenoma; carcinoma)

HYPERTHYROIDISM II

- CAUSES OTHER
  - TSH producing pituitary lesions
  - TRH producing lesions
    • Hypothalamic
    • Ectopic

HYPERTHYROIDISM III

- CAUSES OTHER
  Factitious
  Iatrogenic
  Generalized resistance to thyroid hormone
  HCG producing lesions (mole; chorioca)
HYPERTHYROIDISM IV

• CAUSES OTHER
  “Mechanico-destructive” lesions
  a. Malignant tumors-lymphoma, anaplastic cancer, metastases
  b. Subacute thyroiditis

PAPILLARY NODULE

• Also called papillary hyperplastic nodule
• Also called follicular adenoma with papillary hyperplasia
• May be functional
• Usually solitary
PAPILLARY HYPERPLASTIC NODULE

• PATHOLOGY
  – Encapsulated
  – Centrally cystic
  – Papillary growth
  – Broad papillae
  – Usual nuclei

PAPILLARY HYPERPLASTIC NODULE

• Usually young girls (often near menarche)
• 2-3 cm
• Warm or hot if do radioiodine scan
• Subclinical hyperthyroidism (20%)
• Overt hyperthyroidism (5-10%)

PAPILLARY HYPERPLASTIC NODULE

• REMEMBER
• Papillary thyroid carcinoma rarely if ever functions.
PAPILLARY THYROID CARCINOMA

— Clinical
  • Any age
  • Microscopic to large
  • Female: Male 2-4:1
  • Radiation history
  • Lymph nodes
  • Prognosis 95% at 25 years

PAPILLARY THYROID CARCINOMA

— Gross
  • Any size
  • Confined or extrathyroidal
  • May show capsule (especially follicular variant)
  • May be cystic
  • May note gross calcification or even bone
PAPILLARY THYROID CARCINOMA

— Pathology
  • Papillae and/or follicles
  • Can be totally follicular
  • Sclerosis
  • Calcification (psammoma bodies)
  • NUCLEI

PAPILLARY THYROID CARCINOMA

• THE NUCLEI
  — Elongated
  — Enlarged
  — Cleared out center
  — Thick nuclear membrane
  — Grooves
  — Inclusions
  — Tiny nucleoli
PAPILLARY THYROID CARCINOMA

- Psammoma bodies
  - GHOSTS of dead Papillae
  - In stroma or lymphatics
  - Importance in lymph nodes
PAPILLARY THYROID CARCINOMA

• PATHOLOGY
  • Lymphatic invasion early on
  • May show vascular invasion also
  • Lymph nodes positive over 50% at diagnosis
  • May present as nodal metastasis in neck especially cystic (confused with branchial cleft cyst)

PAPILLARY THYROID CARCINOMA

• SUBTYPES
  — Encapsulated
  — Cystic
  — Microcarcinoma

  — PROGNOSIS BETTER THAN USUAL PTC
PAPILLARY THYROID CARCINOMA

• MICROCARCINOMA
  — DEFINITION:
  — A cancer whose size is 1 cm or less (usually papillary)


PAPILLARY THYROID CARCINOMA

• MICROCARCINOMA

• SURGICAL FINDING:
  — IF ONE FOCUS CONFINED TO THYROID AND FOUND IN LOBE REMOVED FOR A BENIGN LESION, NOTHING FURTHER NEED BE DONE.
PAPILLARY THYROID CARCINOMA

• MICROCARCINOMA:
• QUESTIONS—
  — WHAT IF MORE THAN ONE FOCUS?
    ONE CM RULE
  — WHAT IF INVOLVES THYROID “CAPSULE”? 

PAPILLARY THYROID CARCINOMA

• MICROCARCINOMA
• SURGICAL FINDING:
• IN THYROID REMOVED FOR NODAL METASTASES, THIS IS CLINICAL CANCER AND TREATMENT SHOULD BE APPROPRIATE

PAPILLARY THYROID CARCINOMA

• SUBTYPES
  — TALL CELL
  — COLUMNAR
  — DIFFUSE SCLEROSIS VARIANT
  — SOLID VARIANT
  — HOBNAIL CELL VARIANT
  — MICROPAPILLARY VARIANT
  — PROGNOSIS WORSE THAN USUAL PTC
PAPILLARY THYROID CARCINOMA

• TALL CELL VARIANT
  – Approximately 10-15% of PTC
  – Older patients
  – Large tumors
  – Extrathyroidal
  – Vascular invasion
  – 25% mortality at ten years
PAPILLARY THYROID CARCINOMA

• TALL CELL VARIANT
  • DEFINED AS 50% TALL CELL PATTERN
    — PARTIAL VS TOTAL
    — MEANING OF RECOGNIZING SMALL AMOUNT TALL CELL VARIANT
    — RECURRENCES AND NODAL METS
    — DEDIFFERENTIATION

PAPILLARY THYROID CARCINOMA

• TALL CELL VARIANT
  — Often underrecognized
  — At least 40% of tall cell histology is not noted—especially those tumors with focal tall cell features
  — These cases in recurrences or nodal mets often have a larger percentage of tall cell histology.

  Montone, K et al 2010 USCAP.

PAPILLARY THYROID CARCINOMA

• TALL CELL WARTHIN LIKE PTC
  Series: 21 cases.
  — Wartbin-like PTC has prognosis of usual PTC
  — Some Warthin’s lesions at periphery show loss of lymphoplasmacytic infiltrate and become tall cell
  — The latter extend extrathyroidally, have more frequent nodal metastases and behave like tall cell tumors.
  — Some of the latter (10% in our series) had anaplastic transformation from the tall cell component of the tumor.

  Montone, K et al 2011 USCAP.
PAPILLARY THYROID CARCINOMA

• COLUMNAR CELL VARIANT
  – Less than 5% of PTC
  – Men
  – Extrathyroidal
  – Secretory look
  – Stratified nuclei
  – Bad prognosis if extrathyroidal

NOTE

STRATIFIED NUCLEI
PAPILLARY THYROID CARCINOMA

• COLUMNAR CELL VARIANT
  – Eleven cases complete or > 50% columnar
  – 54% stained for CDX2

  – CDX2 is a nuclear transcription factor important in intestinal development.

  – Columnar cells resemble adenomatous intestinal epithelium

PAPILLARY THYROID CARCINOMA

• COLUMNAR CELL VARIANT
  – Staining of thyroid TMA with numerous benign and malignant nodules all negative for CDX2
  – Meaning of this finding in thyroid unknown

  – Enriquez et al (manuscript submitted 2011)
PAPILLARY THYROID CARCINOMA

• DIFFUSE SCLEROSIS VARIANT
  – Teenagers, usually female
  – Goiter +/- mass
  – Hard, calcified
  – Lymphatics
  – Psammoma bodies
  – Lung mets 25%
  – Prognosis?
PAPILLARY THYROID CARCINOMA

- SOLID VARIANT (SOLID-FOLLICULAR VARIANT)
- Pediatric age group
- Radiation (Chernobyl)
- Ret/PTC 3
- Vascular invasion
- Prognosis?
PAPILLARY THYROID CARCINOMA

- SOLID VARIANT (SOLID-FOLLICULAR VARIANT)
- Can it occur in adults?
- Relationship to autoimmunity?

PAPILLARY THYROID CARCINOMA

- HOBNAIL SUBTYPE
  - Eight cases, predominantly women
  - Average age 57
  - Average size 2.5 cm
  - ETE (50%) cervical nodes (75%)
  - Braf mutated (57%)
  - DOD (50%) at 3.5 yrs
  - Additional 2 patients AWD.

  (Asioli et al AJSP 2010)
PAPILLARY THYROID CARCINOMA

- MICROPAPILLARY TYPE
- VERY RARE BUT Similar to this histology in other organs—breast, ovary, bladder
- Do very poorly
- Over 50% mortality at 5 years
- Early access to lymphatics
- Then disseminate widely.
POORLY DIFFERENTIATED PAPILLARY CARCINOMA

• There are two major subtypes
• Tumors can be poorly differentiated by:

  • HISTOLOGIC PATTERN  Turin 2007
  • GRADING  (Akslen & LiVolsi; Tallini)

POORLY DIFFERENTIATED PAPILLARY CARCINOMA

• HISTOLOGIC PATTERN  Turin 2007
• Solid, trabecular or “insular”
• Mitoses easily found
• Abnormal mitoses
• Necrosis
POORLY DIFFERENTIATED PAPILLARY CARCINOMA

- HISTOLOGIC PATTERN Turin 2007
- Often have well differentiated tumor at edge
  - Papillary
  - Follicular variant
  - Follicular

POORLY DIFFERENTIATED PAPILLARY CARCINOMA

- HISTOLOGIC PATTERN Turin 2007
- Often large tumors
- ETE
- Vascular invasion
- Mortality 50% or >> at 5 yrs
FOCAL FOLLICULAR PATTERN

POORLY DIFFERENTIATED PATTERN

VASCULAR INVASION

VASCULARITY
POORLY DIFFERENTIATED THYROID CARCINOMA

- **GRADING**
- Less well known or studied
- These tumors are recognizable by pattern as papillary, follicular, Hurthle
- Have “bad” features—necrosis, mitoses, much vascular invasion

MOLECULAR TESTING IN THYROID CANCER

- Braf
- RET/PTC
- RAS

MOLECULAR TESTING IN THYROID CANCER

- DIAGNOSIS AND FNA
- PROGNOSIS
PAPILLARY THYROID LESIONS

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